PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
SPW0404 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/050680	16.02.2005	19.02.2004

International Patent Classification (IPC) or national classification and IPC
C07D233/28, A61K31/4164

Applicant
SOLVAY PHARMACEUTICALS B.V.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.07.2005	16.11.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Scruton-Evans, I

Telephone No. +49 89 2399-8272

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/050680

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-19 as originally filed

   Claims, Numbers

   1-10 received on 06.07.2005 with letter of 27.06.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/050680

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the Search Report are referred to in this communication;

D1: WO 03/026647 A (TIPKER JACOBUS ;HERREMANS ARNOLDUS H J (NL); KRUSE CORNELIS G (NL)) 3 April 2003 (2003-04-03)

D2: WO 03/027076 A (HERREMANS ARNOLDUS H J ;KRUSE CORNELIS G (NL); LANGE JOSEPHUS H M) 3 April 2003 (2003-04-03)

D3: WO 03/078413 A (MCCREARY ANDREW C ;DIJKSMAN JESSICA A R (NL); HERREMANS ARNOLDUS H) 25 September 2003 (2003-09-25)

D4: LANGE J H M ET AL: 'SYNTHESIS, BIOLOGICAL PROPERTIES, AND MOLECULAR MODELING INVESTIGATIONS OF NOVEL 3,4-DIARYLPYRAZOLINES AS POTENT AND SELECTIVE CB1 CANNABINOID RECEPTOR ANTAGONISTS' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 47, no. 3, 2004, pages 627-643, XP001188902 ISSN: 0022-2623

D5: WO 03/101969 A (UNIV MICHIGAN) 11 December 2003 (2003-12-11)

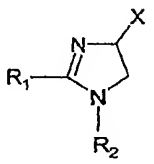
With regard to the requirement for novelty (Article 33(2) of the PCT), for the claimed subject matter, but only compounds of formula I, their salts and tautomers and stereoisomer, the following assessment is made;
D1 and D4 discloses compounds which differ from formula I in that they are dihydropyrazoles, D2 in that they are imidazoles, D3 in that they are thiazoles and D5

in the nature of the group R2.
Article 33(2) of the PCT thus appears to have been satisfied.

With regard to the requirement for inventive step (Article 33(3) of the PCT), for the compounds of claim 1 the problem underlying the present application can be seen as the provision of further novel compounds with CB1 receptor activity. The prior arts D1-D4 all disclose compounds with the same qualitative activity. Certain structural characteristics are shared by these prior art compounds, but D2 is considered to represent the closest prior art. The man skilled in the art, faced with the problem as defined above, may have considered the dihydroderivatives of D2 as a possible solution, but it cannot be said with any degree of accuracy that he would have been unambiguously led to these compounds, especially given that imidazolidines of D5 have a different qualitative activity. Thus for those compounds prepared and tested, and a reasonable generalisation thereof, an inventive step could be acknowledged.

PCT/EP2005/050680: CLAIMS (as amended on June 24, 2005, clean copy)

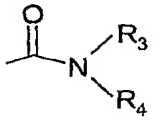
1. Compounds of the general formula (I)



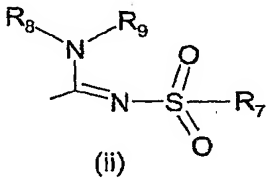
(I)

wherein:

- R_1 and R_2 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1; 2 or 3 substituents Y, which can be the same or different, from the group branched or linear C_{1-3}-alkyl or C_{1-3}-alkoxy, phenyl, hydroxy, chloro, bromo, fluoro, iodo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_1 and/or R_2 represent naphtyl,
- X represents one of the subgroups (i) or (ii),



(i)



(ii)

wherein:

- R_3 represents a hydrogen atom or a branched or linear C_{1-3} alkyl group,
- R_4 represents a branched or linear C_{1-8} alkyl or C_{3-8}-cycloalkyl-C_{1-2}-alkyl group, branched or linear C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenoxy, benzyl, phenethyl or phenylpropyl group, optionally substituted on their phenyl ring with 1-3 substituents Y, wherein Y has the abovementioned meaning, or R_4 represents a pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein

R_5 and R_6 - together with the nitrogen atom to which they are attached -form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from

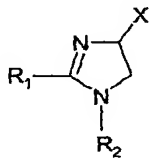
the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom, or

R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, amino, hydroxy or trifluoromethyl group or a fluoro atom,

- R_7 represents a benzyl, phenyl, thienyl or pyridyl group, which groups may be substituted on their aromatic ring with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_7 represents C_{1-8} branched or linear alkyl, C_{3-8} alkenyl, C_{3-10} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl or C_{5-8} cycloalkenyl or R_7 represents naphtyl or R_7 represents a amino group or R_7 represents a C_{1-8} dialkylamino group, a C_{1-8} monoalkylamino group or a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom,
- R_8 represent a hydrogen atom or a methyl group,
- R_9 represents a hydrogen atom or a methyl, ethyl or methoxy group,

and tautomers, stereoisomers and salts thereof

2. Compounds as claimed in claim 1 of the general formula (I)

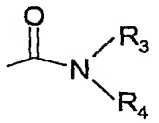


(I)

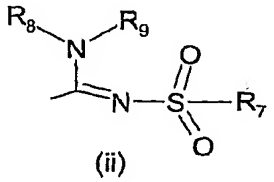
wherein:

- R_1 and R_2 independently represent phenyl, which phenyl group may be substituted with 1, 2 or 3 substituents Y, having the meanings as given in claim 1, or R_1 and/or R_2 represent naphtyl, thienyl or pyridyl,

- X represents one of the subgroups (i) or (ii),



(i)



(ii)

wherein:

- R_3 represents a hydrogen atom,
- R_4 represents a branched or linear C_{1-8} alkyl, branched or linear C_{1-8} alkoxy or C_{3-8} cycloalkyl group, which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenoxy, pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein
  R_5 and R_6 - together with the nitrogen atom to which they are attached -form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) or
  R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a methyl, hydroxy or trifluoromethyl group or a fluoro atom,
- R_7 represents a phenyl group, which phenyl group may be substituted on its aromatic ring with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_7 represents C_{1-8} branched or linear alkyl, C_{3-10} cycloalkyl or C_{5-10} bicycloalkyl, or R_7 represents naphtyl or R_7 represents a amino group or R_7 represents a C_{1-8} dialkylamino group, a C_{1-8} monoalkylamino group or a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl or hydroxy group,

- R_8 represent a hydrogen atom,
- R_9 represents a hydrogen atom

and tautomers, stereoisomers and salts thereof.

3. The compound according to claim 1 which is:

1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(exo-2-bicyclo[2.2.1]heptyl)-4,5-dihydro-1H-imidazole-4-carboxamide (diastereomer A)

1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(exo-2-bicyclo[2.2.1]heptyl)-4,5-dihydro-1H-imidazole-4-carboxamide (diastereomer B)

1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-4,5-dihydro-1H-imidazole-4-carboxamide

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-cyclohexyl-4,5-dihydro-1H-imidazole-4-carboxamide

1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1H-imidazole-4-carboxamidine

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(4-fluorophenyl)-sulfonyl]-4,5-dihydro-1H-imidazole-4-carboxamidine

2-(4-Chlorophenyl)-N-(dimethylaminosulfonyl)-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxamidine

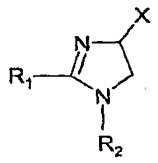
1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(dimethylaminosul-fonyl)-4,5-dihydro-1H-imidazole-4-carboxamidine

4. Pharmaceutical compositions comprising, in addition to a pharmaceutically acceptable carrier and/or at least one pharmaceutically acceptable auxiliary substance, a pharmacologically active amount of at least one compound as claimed in any of the claims 1-3, or a salt thereof, as an active ingredient.

5. A compound as claimed in any of the claims 1-3, or a salt thereof, for use in medicine

6. Use of a compound as claimed in any of the claims 1-3, for the preparation of a pharmaceutical composition for the treatment of psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, in particular juvenile obesity and drug induced obesity, addiction, impulse control disorders, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea, cardiovascular disorders, atherosclerosis, liver cirrhosis and sexual disorders.

7. Use of a compound of formula (I):

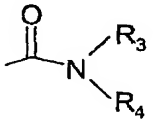


(I)

wherein:

- R_1 and R_2 have the meanings as given in claim 1, but may also independently represent methylsulfonyl,

- X represents the subgroup (i),



(i)

wherein:

- R_3 and R_4 have the meanings as given in claim 1, but in which R_4 may also represent a phenyl group, optionally substituted with 1-3 substituents Y, wherein Y has the meaning as given in claim 1,
  for the preparation of a pharmaceutical composition for the treatment of psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, in particular juvenile obesity and drug induced obesity, addiction, impulse control disorders, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea, cardiovascular disorders, atherosclerosis, liver cirrhosis and sexual disorders.

8. Use as claimed in claim 6 characterized in that said disorders are eating disorders, in particular obesity, juvenile obesity and drug induced obesity.

9. Use of a compound as claimed in any of the claims 1-3 for the preparation of a pharmaceutical composition for the treatment of eating disorders, in particular obesity, juvenile obesity and drug induced obesity, characterized in that said pharmaceutical composition also contains at least one lipase inhibitor.

10. Use as claimed in claim 9, characterized in that said lipase inhibitor is orlistat or lipstatin.